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CHCHD10 mutations and motor neuron disease: the distribution in Finnish patients

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INTRODUCTION

Motor neuron disorders (MNDs) are a heterogeneous group of diseases that result from degeneration of motor neurons. If both upper and lower motor neurons (UMNs and LMNs) are affected, the disease is classified as amyotrophic lateral sclerosis (ALS). Primary lateral sclerosis (PLS) and progressive muscular atrophy (PMA) selectively affect the UMNs or LMNs, respectively, but are sometimes considered to be incomplete ALS variants because their phenotype may evolve into typical ALS over time. Bulbar affection in a UMN disease would favour a diagnosis of PLS over hereditary spastic paraplegia (HSP), whereas rapid progression may separate PMA from adult-onset spinal muscular atrophy (SMA).

Some SMA-like or even ALS-like phenotypes have been incorporated into the large category of sensorimotor axonal neuropathies (Charcot-Marie-Tooth disease type 2, CMT2),[1] although sensory abnormalities may be subtle in some forms.[2] On the other hand, spinal and bulbar muscular atrophy (Kennedy disease) is classified as a form of adult-onset SMA despite prominent sensory abnormalities. It has recently been argued that the current classification system of MNDs is unsatisfactory and should be revised to include genetically and prognostically important categories.[3]

We have recently identified a new form of motor neuron disease in 55 patients from 17 Finnish families, where distinctive phenotype did not match any pre-existing neuromuscular disease category.[4–6] Spinal muscular atrophy Jokela type (SMAJ, OMIM #615048) is characterised by painful cramps, fasciculations, decreased or absent tendon reflexes, elevated creatine kinase and hand tremor. The first symptoms appear commonly after age 30–40. Electromyography (EMG) and muscle biopsy display widespread neurogenic findings and a proportion of patients show sensory abnormalities. Muscle weakness and atrophy appear much later in the disease course, and patients have remained ambulant for several decades and their life expectancy is within normal range.[4 5] SMAJ is caused by a dominant *CHCHD10* mutation c.197G>T p.G66V, a founder mutation in the Finnish population.[6] All Finnish patients reported so far carry the same mutation that is linked to the same disease-associated haplotype.[5–8]

Since the original report in 2014,[9] dominant mutations in *CHCHD10* have been identified to cause a wide range of neurological disorders. Certain mutations have been reported to cause distinct phenotypes such as c.176C>T p.S59L causing frontotemporal dementia (FTD)-ALS with mitochondrial myopathy,[9] c.172G>C p.G58R isolated mitochondrial myopathy[10] and c.197G>T p.G66V SMAJ[6] or CMT2.[8] However, the pathogenicity of most of the reported mutations has remained uncertain because the segregation has not been proven and/or functional studies have not been available.[11–16] So far, most *CHCHD10* studies have been concentrated on patients with ALS, although other phenotypes, such as SMAJ, seem to be more prevalent among the ascertained mutations.

Although CHCHD10 is a mitochondrial protein and other mutations in *CHCHD10* have been reported to be associated with mitochondrial myopathy, no significant mitochondrial muscle pathology has been detected in patients with SMAJ.[17] However, in a Finnish cohort of 126 families referred with CMT2 diagnosis, 4.8% had the c.197G>T p.G66V mutation and low levels of mitochondrial DNA (mtDNA) deletions were suspected in some.[8]

In this study, we screened several cohorts of Finnish patients with distinct neurogenic disorders and one cohort of mitochondrial myopathy in order to clarify the presence of *CHCHD10* mutations as well as their phenotypic manifestations. To further study the possible mtDNA instability due to c.197G>T p.G66V mutation, we compared the amount of mtDNA deletions in 10 patients with SMAJ to that of 9 patients with other genetically confirmed MNDs.

METHODS

Patients

Three hundred and thirty six Finnish patients with distinct neurogenic disorders at our quaternary referral centre in Finland were selected for sequencing of the *CHCHD10* gene. Of the patients included in the study, 215 had lower motor neuron syndrome (LMNS) similar to SMAJ, with or without some sensory abnormalities. Five of these patients had an initial clinical diagnosis of CMT2 but with atypical features more suggestive of SMAJ, such as normal compound muscle action potential (CMAP) values despite widespread neurogenic abnormalities, or prominent creatine kinase elevations up to 1800 U/L. Of the other patients, 28 had HSP, 24 patients had a non-specified neurogenic disorder, 14 patients had mitochondrial myopathy and 55 patients had a diagnosis of ALS according to the El Escorial criteria with involvement of

Table 1 Patient cohorts included in the study

Disorder	Number of patients	Clinical features
LMNS	215	Predominantly lower motor neuron disease, including patients with atypical CMT2 (SMAJ-like phenotype)
ALS	55	Signs of UMN and LMN involvement
Non-specific neurogenic	24	Cramp-fasciculation syndrome, no widespread weakness, neurogenic findings on EMG and/or muscle biopsy
HSP	28	No signs of LMN involvement
Mitochondrial myopathy	14	Muscle histology compatible with mitochondrial disease

ALS, amyotrophic lateral sclerosis; CMT2, Charcot-Marie-Tooth disease type 2; EMG, electromyography; HSP, hereditary spastic paraplegia; LMN, lower motor neuron; LMNS, lower motor neuron syndrome; UMN, upper motor neuron.

UMN and LMN. Clinical features of the patient cohorts are presented in table 1.

In the patients with ALS, mutations in *SOD1* and *FUS* as well as the repeat expansion mutation in *C9orf72* had been previously excluded. For 23 of the patients with ALS, *TARDBP* had also been sequenced with normal findings. For patients with HSP, 33 known disease genes were screened by a targeted next-generation sequencing panel prior to this study (as described in Ylikallio *et al*[18]), without causative findings. The possible family history of the patients was not clarified before the study. The studies were approved by local ethical committees and all samples were obtained with informed consent.

Molecular genetic analyses

Genomic DNA was extracted from venous blood according to standard procedures. For all patients, we sequenced exon 2 of *CHCHD10* that harbours all pathogenic mutations reported so far. Additionally, in 103 patients, the rest of the coding region of the gene was also sequenced. Of these patients, 79 belonged to the LMNS group, 2 had mitochondrial myopathy, 15 had a non-specified neurogenic disorder and 7 had ALS. Primer sequences of the exons studied were designed to include the entire exon and exon–intron borders and are available on request. The regions studied were amplified by PCR (Thermo Scientific Fermentas PCR Master Mix; MBI Fermentas, Amherst, New York, USA) and directly sequenced using a Big-Dye Terminator V.3.1 Kit on an ABI3130xl automatic DNA Genetic Analyzer (Applied Biosystems, Foster City, California, USA). Sequences were analysed with Sequencher V.5.1 software (Gene Codes Corporation, Ann Arbor, Michigan, USA). For patients with HSP, the sequencing was done as described in Auranen *et al*.[8]

MtDNA analysis

For analysis of mtDNA deletions, we selected 10 patients with previously proven SMAJ and 9 patients with other genetically defined MNDs. Mitochondrial pathology on a light microscopic level was minor (1–2% COX-negative fibres) in the patients with SMAJ and only present in half (5/10) of the muscle biopsies. The group of other genetically defined MNDs consisted of three patients with ALS-FTD caused by *C9orf72* repeat expansion mutation (two with minimal mitochondrial pathology, one without), five patients with Kennedy disease (two with minimal mitochondrial pathology, three without) and one patient with ALS caused by a homozygous c.272A>C p.D91A mutation in *SOD1*. The age of patients with SMAJ ranged from 41 to 57 years, whereas the ages of the other patients were from 39 to 62 years.

The DNA was extracted from muscle biopsies according to standard procedures. MtDNA deletion load was visualised by long-range PCR as described in Auranen *et al*.[8]

RESULTS

Genetic findings

Heterozygous mutation c.197G>T p.G66V in *CHCHD10* was detected in 23 patients. In two siblings with a cramping disorder and mitochondrial pathology, heterozygous c.100C>T p.P34S was detected. Other mutations were not found.

MtDNA analysis

The results of mtDNA deletion analysis are presented in figure 1. The amount of deletions in SMAJ samples was very low and not higher than in the non-SMAJ samples. Furthermore, no obvious correlation between the amount of deletions and the 'minor mitochondrial' muscle phenotype of the patients was observed.

Clinical characteristics of the patients with *CHCHD10* mutations

Patients carrying the mutation c.197G>T p.G66V had a slowly progressive, proximal and distal motor neuronopathy with reduced tendon reflexes. Age at onset ranged from 25 to

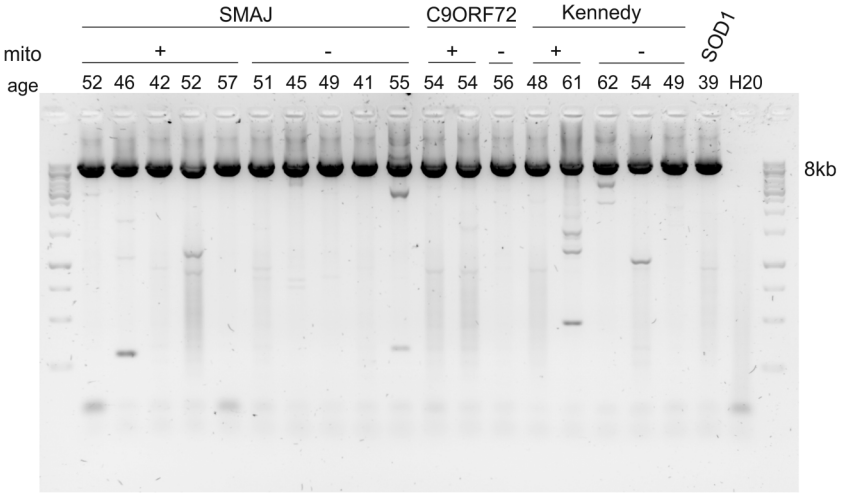

Figure 1 The results of mtDNA deletion analysis in patient groups of four different MNDs. The 8 kb band represents the undeleted mtDNA. Smaller bands correspond to deleted mtDNA molecules. Low levels of mtDNA deletions were observed in all MNDs included in the study, meaning they are not a specific feature of SMAJ. mito+=presence of mitochondrial pathology in muscle biopsies, mito−=absence of mitochondrial pathology in muscle biopsies, age=age of the patient at muscle biopsy, H_2O=non-template PCR. MND, motor neuron disorder; mtDNA, mitochondrial DNA; SMAJ, spinal muscular atrophy Jokela type.

70 years, although one patient reported having always been clumsy (P20). In patient P5, the presenting symptom was reduced distal upper limb function, while in all others, lower limb symptoms predominated. The eldest patients, P2 and P3, still retained some ambulation at the ages of 82 and 86 years. Clinical characteristics of the patients are listed in table 2.

Similar to our previous report,[6] many patients had some reduction in sensory nerve action potential amplitudes (SNAPs), but this was extremely variable. For example, sural SNAPs were severely reduced in an otherwise asymptomatic 28-year-old woman (P12; 4.0 μV and −4.4 SD), while they were normal in a 79-year-old man (P2; 4.5 μV and −0.5 SD) with a disease duration of nearly two decades. In one patient (P8), all sensory amplitudes were severely reduced at the age of 57 (absent sural SNAPs with median, ulnar and radial SNAPs <1 μV), even though the clinical phenotype was typical of SMAJ with areflexia, muscle cramps in all limbs followed by slowly progressive weakness. In contrast to the reduced SNAP values in several patients, CMAP values were nearly always within normal range, although one patient has low amplitude CMAP values (P8; <−2SD) in the upper and lower limbs. None of the patients developed severe foot drop despite very long disease durations of several decades. Lower limb muscle MRI in six patients showed fatty degenerative changes in the calves and posterior thigh muscles. Muscle biopsy obtained in nine patients displayed chronic neurogenic abnormalities with fibre type grouping and groups of normal sized type IIA fibres. Three out of 15 patients (P8, P17, P20) in this cohort showed fibrillations in the first dorsal interosseous muscle, which we previously have also shown to be very rare in SMAJ, as an important distinction from ALS.[19]

Patients carrying c.100C>T p.P34S were siblings who had a cramping disorder with normal tendon reflexes and no neurogenic changes on EMG. Muscle biopsy findings suggested a mitochondrial myopathy. A third sibling with the same clinical and muscle pathology phenotype, however, did not carry the variant. The parents of the siblings were asymptomatic, but their DNA samples were not available for the study.

DISCUSSION

In our cohort of 336 Finnish patients with undetermined MND or mitochondrial myopathy, 23 proved to have the Finnish founder mutation c.197G>T p.G66V in *CHCHD10*. The phenotype of all of them was restricted to SMAJ. Previously, c.197G>T p.G66V mutation carriers have also been identified in a Finnish cohort of patients referred by the clinicians as having CMT2.[8] There is growing evidence that dominantly

Table 2 Clinical characteristics of the patients with heterozygous CHCHD10 mutation c.197G>T p.G66V

Patient	Sex	Age at onset	Symptoms at onset	Age at examination	Inheritance	Walking ability	Neurography/electromyography abnormalities	CK
P1	F	30	Cramps	68	AD	1 km	Age 68: sensorimotor	2–3×
P2	M	60	Cramps	82	Sporadic	Needs a walker	Age 79: sensorimotor (normal sural but reduced upper limb SNAPs)	2×
P3	M	70	Fasciculations	86	AD	Needs a walker	Age 82: sensorimotor (normal sural but reduced upper limb SNAPs)	2–3×
P4	M	25	Cramps	57	AD	Normal	Age 57: sensorimotor	2–3×
P5	F	46	Weakness	67	AD	Normal	Age 42: motor Age 66: sensorimotor	Normal
P6	F	Before age 62	Cramps	66	AD	Normal	Motor	ND
P7	M	42	Weakness, fasciculations	44	AD	Normal	Motor	ND
P8	M	40	Weakness	55	AD	Normal	Sensorimotor	3×
P9	F	25	Cramps	37	AD	Normal	Motor	1.5×
P10	M	42	Weakness	49	Sporadic	Normal	Motor	ND
P11	F	40	Cramps	60	AD	Normal	Motor	ND
P12	F	28	Asymptomatic with absent tendon reflexes	52	AD	Normal	Age 28: sensorimotor Age 52: very little progression in sensory findings	ND
P13	M	46	Myalgia	49	AD	Normal	Age 46: sensorimotor	3–6×
P14	F	Before age 42	Cramps	48	AD	Normal	Age 42: motor	2×
P15	F	Before age 60	Cramps	65	AD	Normal	Sensorimotor	2–3×
P16	F	54	Cramps	55	AD	Normal	Age 54: motor	1.5×
P17	M	46	Weakness	55	AD	Normal	Age 53: sensorimotor	2–3×
P18	F	39	Weakness and cramps	59	AD	Normal	Age 39: motor Age 49: sensorimotor	2×
P19	F	Before age 64	Impaired walking/balance	70	AD	Walking sticks	Age 67: motor	ND
P20	F	Childhood?	Clumsiness in childhood, could be unrelated	60	AD	<1 km	Age 60: sensorimotor	ND
P21	F	40	Cramps	58	AD	Normal	Age 58: motor axonal	Normal
P22	M	48	Weakness and fasciculations	51	Sporadic	Normal	Age 51: sensorimotor	1.5–5×
P23	F	58	Weakness	70	AD	Walking sticks	Age 69: Motor axonal	1.5×

AD, autosomal dominant; CK, creatine kinase; F, female; M, male; ND, not detected; SNAP, sensory nerve action potential.

Table 3 Reported variants in CHCHD10

Mutation	Exon	Frequency in ExAC	Reported phenotypes	Number of reported patients	Patient origin	Pathogenic according to functional studies	Segregates with the disease	References	NB
c.34C>T p.P12S	1	0.00001682	ALS	1	Spain	NA	NA	24	
c.43C>A p.R15S*	2	–	MM	10	Puerto Rico	No	Yes	10	
c.44C>A p.R15L	2	–	ALS	13	Germany, USA, Canada	NA	No/yes	11 13 15 26	
c.67C>A p.P23T	2	–	FTLD	1	Italy	NA	NA	15	
c.100C>T p.P34S	2	0.0009654	ALS, FTD-ALS, PD, AD	15	France, Italy, Canada, Australia	NA	No	12 14–16 27	Indications that the variant is not pathogenic[15 16]
c.104C>A p.A35D	2	–	FTLD	1	Italy	NA	NA	15	
c.172G>C p.G58R*	2	–	MM	10	Puerto Rico	Yes	Yes	10	
c.176C>T p.S59L	2	–	FTD-ALS with MM	9	France, Spain	Yes	Yes	9 12	
c.197G>T p.G66V	2	–	SMAJ, CMT2	73	Finland	NA	Yes	6 8 11 23	
c.239C>T p.P80L	2	0.0003461	ALS	4	Italy, Canada	NA	Possibly	14 15	Small number of patients
c.244C>T p.Q82X	2	0.00004243	FTD	1	Spain	NA	NA	24	

The variants have been annotated according to transcript NM_213720.
AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; CMT2, Charcot-Marie-Tooth disease type 2; FTD, frontotemporal dementia; FTLD, frontotemporal lobar degeneration; MM, mitochondrial myopathy; NA, not assessed; PD, Parkinson's disease; SMAJ, spinal muscular atrophy Jokela type.
*Mutations *in cis*.

inherited mutations in other genes that cause SMA may also cause CMT2. At least mutations in *HSPB1*, *MFN2* and *DYNC1H1* do not cause distinct entities but a continuum of phenotypes ranging from SMA to CMT2.[20–22] As we have reported previously, SNAP reductions may occur in patients with SMAJ,[5 6] despite almost no clinical evidence of sensory dysfunction. In our experience, patients with SMAJ typically show clinical and/or EMG findings in a proximal and distal distribution already at the initial investigations, in contrast to CMT2, where disease progression to proximal muscles is a late phenomenon. In this respect, SMAJ is more similar to Kennedy disease (although with absent bulbar signs). Even though c.197G>T p.G66V has been reported in the literature to cause ALS,[8 23–25] all these reports erroneously reference one family reported by Müller *et al*[11] as ALS. In fact, this Finnish family was defined with a motor neuron disease without stated UMN findings, and this family was later detailed in our SMAJ cohort as not having ALS.[6] We nevertheless consider SMAJ to be an important differential diagnostic alternative in patients with a neurogenic disorder suggestive of CMT2 or ALS, because in routine clinical practice without highly detailed analysis, patients with SMAJ have received both of these diagnoses before the final molecular diagnosis.

Two patients, a brother and a sister, carried the variant c.100C>T p.P34S, but their third similarly affected sibling was not a carrier. Since the variant c.100C>T p.P34S did not segregate with the disease in this family, it is not likely to be disease causing. This is also supported by the reports of Zhang *et al*[15] and Dobson-Stone *et al*[16] who showed that c.100C>T p.P34S is present in a normal population with a considerable frequency.

Mutation c.100C>T p.P34S is one of many *CHCHD10* mutations suggested to be pathogenic based on their absence from international variant databases (table 3). Further evidence is required, however, because most variants at the 5′ end of *CHCHD10* exon 2 are not included in variant databases due to low coverage of that area in exome sequences.[16] As the quality and number of exome sequences increase, it is probable that many of the reported *CHCHD10* variants appear to have some kind of frequency in a normal population making their pathogenic role more unlikely. Out of 11 *CHCHD10* variants reported, at least 4 have received a frequency in the ExAC database (table 3), after the first reports of their possible pathogenicity. Since the population frequency seems to depend both on time and the population studied, it is not recommendable to call a variant pathogenic based on the population frequency alone.

Our results suggest that c.197G>T p.G66V is a common mutation in Finland, with 93 patients reported so far. In the SISu database V.3.0 (http://www.sisuproject.fi) of 6104 Finnish individuals, c.197G>T p.G66V has been identified once. On the basis of the number of our determined patients and the SISu frequency, we estimate the prevalence of c.197G>T p.G66V to be around 2–4/100 000 in Finland. Other mutations in *CHCHD10* are not common, at least not in the Finnish population. Our results also provide further evidence that pathogenic mutations in *CHCHD10* are concentrated in exon 2, as previously reported (see table 3).[12 13 27]

So far, only three mutations in *CHCHD10* have strong evidence for causality. Two of these, c.176C>T p.S59L and c.172G>C p.G58R, have been associated with mitochondrial myopathy and mtDNA instability.[9 10] CHCHD10 protein is part of the mitochondrial mitochondrial contact site and cristae organizing system (MICOS) complex, which is involved in cristae organisation and thus mtDNA nucleoid maintenance.[28] However, the patients carrying c.197G>T p.G66V have not presented signs of mitochondrial myopathy and mitochondrial pathology has not been considerable in their muscle biopsies. In this study, we compared the amount of mtDNA deletions in 10 patients with SMAJ with 9 patients with other genetically defined MNDs. No significant increased amount of mtDNA deletions could be observed in the patients with SMAJ, supporting that mitochondrial pathology is not a feature of the SMAJ phenotype.

In general, *CHCHD10*-related disorders seem to be rare worldwide. So far, only three mutations causing three distinct

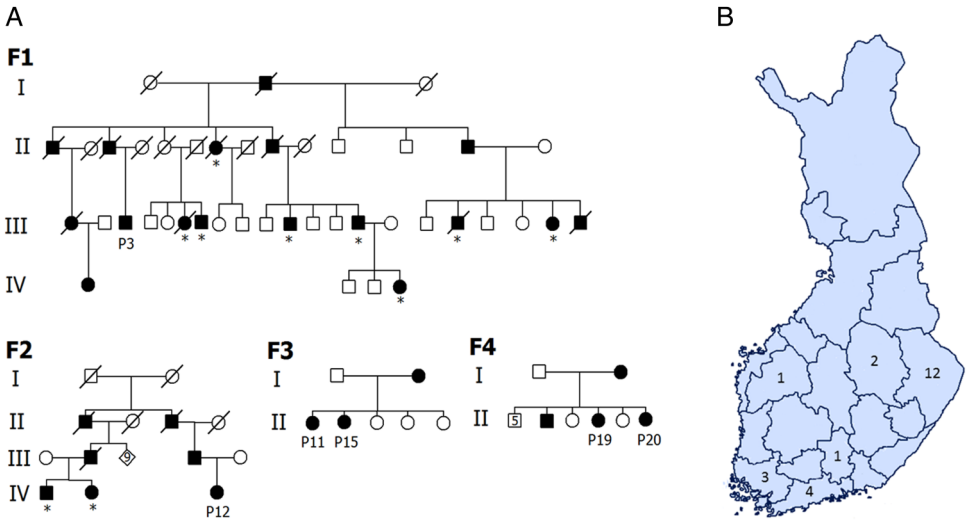

Figure 2 Genealogical information of the patients with SMAJ found in this study. (A) Pedigrees of the patients related to other known patients with SMAJ. The patients reported previously have been marked with an asterisk. (B) Distribution of the patients with SMAJ (total 23) found in this study between Finnish hospital districts. SMAJ, spinal muscular atrophy Jokela type.

phenotypes have been reported, with other findings still requiring further evaluation (table 3). Of the ascertained *CHCHD10*-related disorders, SMAJ is by far the most frequent disease. This is at least in part due to the enrichment of the founder mutation in the genetically isolated Finnish population. Genealogical information of the patients with SMAJ found in this study was clarified retrospectively. Patient P3 was found to belong to a family reported by Pasanen *et al*[23] and patient P12 was related to a family reported by Penttilä *et al*.[6] Patients P11 and P15 are sisters, as are patients P19 and P20 (figure 2A). No relations between other patients to each other or to the previously known families were found. However, owing to the founder effect of the c.197G>T p.G66V mutation in the Finnish population, it is evident that all Finnish patients carrying the mutation have a common ancestry, probably of Northern Karelian origin (figure 2B). The presence of SMAJ in other populations still needs further studies but, considering the large numbers of Finnish emigrants to different countries during the past 150 years, SMAJ should exist in some descendants. Furthermore, *CHCHD10* mutations have mostly been evaluated in ALS cohorts and it is possible that *CHCHD10* mutations are more prevalent in other disease types. Cohorts of patients with adult-onset lower MNDs, including Kennedy disease phenocopies, should be screened for *CHCHD10* mutations.

Our results support the hypothesis that *CHCHD10* mutations have a relatively strict genotype–phenotype correlation. However, more studies in different cohorts are definitely needed as well as further functional studies to elucidate how the different mutations result in the particular phenotypes.

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Contributors SP drafted the manuscript, acquired the data and performed the analysis. MJ, JP, JL and MA characterised the patients and edited the manuscript. AMS, JT and SS characterised the patients. MS acquired the data. EY and HT acquired the data and edited the manuscript. BU conceived the study, characterised the patients and edited the manuscript.

Competing interests None declared.

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CHCHD10 mutations and motor neuron disease: the distribution in Finnish patients

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